

Remarks

Claims 53, 55 – 58 and 61 - 64 are active in the case. Claims 53 is the only independent claim. Claim 59 has been cancelled and inserted into claim 53. Support for the amendments is also found at [0045] (3500 to 6,000 mg total weight), and [0023] (alendronate).

The present invention relates to an improved method for treating osteoporosis with an effervescent bisphosphonate solution having high buffering capacity, combined with an anti-ulcer agent. As shown by the Rule 132 Declarations submitted herewith, absorption of alendronate is enhanced by highly buffered effervescent formulations, as claimed.

The Rejection of Claims under 35 U.S.C. § 103

Claims 53 – 64 stand rejected under 35 U.S.C. § 103 as being obvious over Katdare et al. (US 5,853,759) in view of Daifotis (U.S. 5,994,329). Katdare teaches that bisphosphonates can be administered in effervescent solutions, but does not disclose or suggest the beneficial effects of highly buffered solutions on absorption of the drug. Example 8 of Daifotis et al. is a liquid composition of alendronate but not an effervescent one, and so did not suggest anything about highly buffered effervescent formulations of the drug.

In order to show the effects of buffering capacity in effervescent formulations, applicants submit herewith an executed Second Declaration under 37 CFR 1.132 by Marshall A. Hayward, Ph.D., who directed a human clinical trial to show the bioequivalence between EX101, a highly buffered effervescent formulation containing 70 mg of alendronate (ALN), and commercial 70 mg Fosamax tablets from Merck & Co.

Furthermore, in order to show that highly buffered effervescent formulations improve the absorption characteristics and dosing consistency of alendronate compared to conventional effervescent formulations, such as those taught in Katdare (U.S. 5,853,759; "Katdare"), Dr. Hayward analyzed data published in a study conducted by Merck & Co. that was submitted to the FDA as part of a New Drug Application (NDA). The results of that Merck NDA are available to the public (in redacted form) under the Freedom of Information Act, a copy of which is attached to his Declaration.

In addition, applicants submit herewith a first Declaration under 37 CFR 1.132 by Dr. Hayward (executed December 15, 2003) and a Declaration under 37 CFR 1.132 by Till Rohrich, Ph.D. (executed December 15, 2003, which were both submitted in co-pending application 09/092,083. These declarations related to the buffering capacity of the examples in Katdare.

Two different dosage levels are discussed in the Second Hayward Declaration -- (1) EX101 (70 mg ALN), and (2) a 10 mg effervescent formulation tested by Merck, which is representative of Katdare in Dr. Hayward's opinion, since the buffering levels are similar to the examples of Katdare (Second Hayward Decl. ¶4)

It is desirable for a dosing form to be as consistent and predictable as possible. Data in the Second Hayward Declaration show that EX101 is a superior formulation to the conventional effervescent formulation of Kadare because the highly buffered one has a significantly lower coefficient of variation (CV) with respect to the mean absorption level. In other words, drug absorption from the EX101 formulation shows lower variability than would be available from the formulations of Katdare. (Second Hayward Decl. ¶10 -11). Table 1 from the declaration is

reproduced below. It shows that the highly buffered EX101 provides a much improved coefficient of variation compared to the Merck effervescent, i.e., 57% vs. 82%

Table 1: Coefficients of variation (CV) of EX101 vs. Merck's Effervescent form

Parameter	EX101	Merck Effervescent 10 mg tablet reference	Comment
Mean Alendronate Absorption Coefficient of variation (CV)%	57%	82%	EX101 shows significantly less variation than Merck's effervescent form

The coefficient of variation is a measure of variability, hence the highly buffered formulations of the present invention demonstrate significantly less variability. Accordingly, as now presented, the claims would not have been obvious within the meaning of 35 USC 103.

Conclusions

Applicants submit that the case is now in condition for allowance. Early notice to that effect is earnestly requested.

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If it is deemed helpful or beneficial to the efficient prosecution of the present application,
the Examiner is invited to contact Applicant's undersigned representative by telephone.

Respectfully submitted,

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